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SPECIAL COMMUNICATION

Clinical Use of Neuromuscular Electrical Stimulation for Neuromuscular Rehabilitation: What Are We Overlooking?

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Abstract
The clinical success of neuromuscular electrical stimulation (NMES) for neuromuscular rehabilitation is greatly compromised by the poor consideration of different physiological and methodological issues that are not always obvious to the clinicians. Therefore, the aim of this narrative review is to reexamine some of these fundamental aspects of NMES using a tripartite model perspective. First, we contend that NMES does not actually bypass the central nervous system but results in a multitude of neurally mediated responses that contribute substantially to force generation and may engender neural adaptations. Second, we argue that too much emphasis is generally placed on externally controllable stimulation parameters while the major determinant of NMES effectiveness is the intrinsically determined muscle tension generated by the current (ie, evoked force). Third, we believe that a more systematic approach to NMES therapy is required in the clinic and this implies a better identification of the patient-specific impairment and of the potential "responders" to NMES therapy. On the basis of these considerations, we suggest that the crucial steps to ensure the clinical effectiveness of NMES treatment should consist of (1) identifying the neuromuscular impairment with clinical assessment and (2) implementing algorithm-based NMES therapy while (3) properly dosing the treatment with tension-controlled NMES and eventually amplifying its neural effects.
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Electrical stimulation therapy consists of delivering preprogrammed trains of stimuli to nerves, muscles, or joints via surface electrodes positioned on the skin, with the ultimate goal to provide an acute and/or chronic therapeutic effect. Depending on current characteristics and electrode locations, 3 main electrotherapy modalities can be distinguished:

1. Transcutaneous electrical nerve stimulation, which consists of the application of a low-intensity and continuous electrical current to the cutaneous nerve fibers with no apparent muscular involvement; this modality is mainly used for acute and chronic pain treatment (benefits are obtained during and after stimulation)
2. Functional electrical stimulation, which consists of the application of a moderate-intensity and cyclic electrical stimulation to the selected muscles; this modality is mainly used to generate functional movements that mimic voluntary contractions and to restore functions that have been lost (benefits are mainly obtained during stimulation)
3. Neuromuscular electrical stimulation (NMES), which consists in the application of high-intensity and intermittent electrical stimuli to generate relatively strong muscle contractions, most often in isometric tetanic conditions (even if nontetanic alternatives exist)[1-3]; this modality is mainly used for

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neuromuscular rehabilitation/strength training (benefits are mainly obtained after repeated sessions).

Despite controversial scientific results, the first 2 modalities can be considered as successfully integrated into the clinical settings, respectively, for pain-related and neurological rehabilitation. In contrast, NMES still suffers from poor clinical acceptability for neuromuscular rehabilitation,[4-8] despite a growing body of scientific evidence in its favor.

NMES has the potential to be used in different populations for neuromuscular rehabilitation/strength training with different goals (fig 1):

1. Maintaining/preserving neuromuscular function *during* disuse induced, for example, by an injury, a disease, or simply by the aging process (see, eg, Gibson et al[9])
2. Restoring neuromuscular function *after* disuse, for example, as a result of an injury and/or surgery (see, eg, Snyder-Mackler et al[10])
3. Improving neuromuscular function in able-bodied individuals, including athletes (see, eg, Seyri and Maffiuletti[11]).

For patient populations, the ultimate goal is to improve physical function and, in turn, quality of life. In this respect, it is important to clarify that *quadriceps femoris* is the most commonly stimulated muscle (for both practical and functional reasons) and therefore our article will mainly focus on quadriceps NMES therapy for different patient groups.

Besides the use of NMES for strength training in able-bodied individuals and athletes (which is outside the scope of the present article), NMES therapy has previously been used in geriatric patients with sarcopenia,[12-15] those who were critically ill,[4,7,16] those with neurological diseases,[17-19] those with orthopedic problems,[20-22] and those with chronic heart failure and chronic obstructive pulmonary disease,[23-26] but mainly for research purposes. The potential effectiveness of NMES has often been inferred from nontreatment studies evaluating the effect of selected stimulation parameters on muscle response/discomfort,[27-35] while randomized controlled trials are less frequent. A common conclusion from most of the systematic reviews on NMES effectiveness is the tremendous diversity (and lack of consensus) in NMES protocols between the studies,[7,16,17,19,21,22,24-26] which inevitably contributes to the exaggerated heterogeneity in individual response to NMES. We believe that such heterogeneity is largely due to the poor clinical consideration of different physiological and methodological factors in relation with the magnitude of evoked force (ie, the main determinant of NMES effectiveness) (fig 2) that we wish to reexamine in this narrative review. Thus, the 3 main sections of this article will focus on these important but often overlooked aspects of NMES using neurophysiological, methodological, and application perspectives.

What are we overlooking? A neurophysiological perspective

NMES has long been considered as a "peripheral" therapeutic modality for maintaining/rebuilding muscles during/after a period of reduced use, with little or no effect on the central nervous system (CNS). Over the past 2 decades, however, strong evidence has emerged showing that NMES can have substantial effects, both acute and chronic, on a multitude of CNS properties. These findings are especially interesting in light of the fact that some of the patients who could potentially benefit from the peripheral effects of NMES also show neural impairments as a result of their condition (see section on application perspective). In this section, we will first address how and to what extent different spinal and supraspinal structures can be activated in response to a single session or to multiple bouts of NMES. Then, we will focus on whether the modulation of some stimulation parameters could be considered as an attractive strategy for enhancing the magnitude of the afferent volley to the CNS and, in turn, evoked force.

From a neurophysiological perspective, NMES applied to a muscle or a nerve trunk leads to the activation of both cutaneous and muscle sensory fibers (ie, Ia, Ib, II) and to the depolarization of motor neurons. The afferent volley first travels through the spinal cord and then ascends to various brain areas. Accordingly, increased excitability of the corticomotor pathway has been reported in response to a single NMES session,[36] and functional magnetic resonance imaging investigations have revealed cortical and subcortical activation patterns during NMES.[37-39] Interestingly, it should be pointed out that this electrically evoked neuronal network is similar to the one activated by voluntary contractions.[38] Therefore, contrary to the general belief, the acute application of NMES does not actually bypass the CNS neither at

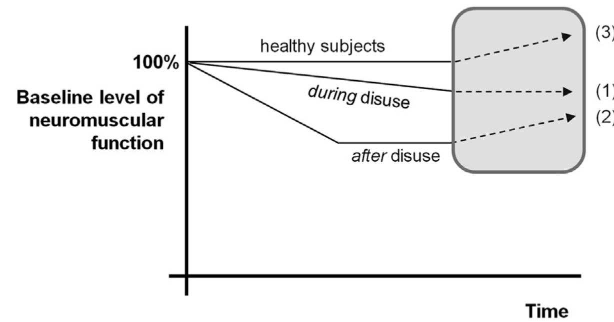

Fig 1 Expected effects of NMES therapy (shaded area) on neuromuscular function in 3 populations: (1) preservation of neuromuscular function in patients during disuse; (2) partial restoration of neuromuscular function in patients after disuse; and (3) improvement of neuromuscular function in able-bodied individuals with "normal" function.

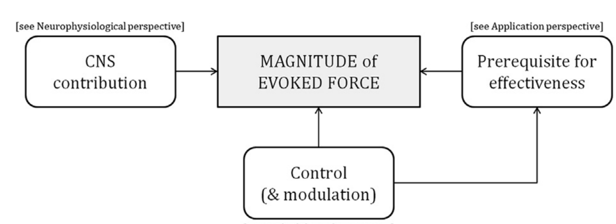

Fig 2 The magnitude of electrically evoked force is the only valid indicator of NMES dose and the main determinant of NMES treatment effectiveness. Thus, the magnitude of evoked force constitutes the thread of the present article and the crossroad between the neurophysiological, methodological, and application perspectives.

List of abbreviations:

CNS central nervous system
MVC maximum voluntary contraction
NMES neuromuscular electrical stimulation

the spinal level nor at the supraspinal level. On that basis, NMES has been used as a tool for inducing activity-dependent neural plasticity in able-bodied individuals. This is illustrated, for example, by training-induced improvements in maximal electromyographic activity and neural activation[40,41] and maximal voluntary strength of the contralateral unstimulated muscle[42] following unilateral NMES programs of 3 to 5 weeks in able-bodied individuals. This cross-education effect combined with the lack of changes in Hoffmann reflex amplitude[40] suggested that the sites of neural adaptation induced by NMES strength training are probably located at the supraspinal level and that NMES-induced repeated activation of sensory fibers might result in a decreased interhemispheric inhibition.[42,43] However, further conditioned transcranial magnetic stimulation and/or magnetic resonance imaging investigations are needed to decipher the role of transcallosal pathways[43] and short intracortical inhibition and facilitation[44,45] in NMES-induced neural adaptations.

It has recently been suggested that the magnitude of the NMES-induced afferent volley to the CNS might be further enhanced by the combined use of relatively low current intensities, long pulse durations, and high frequencies.[46] Briefly, this newly introduced wide-pulse high-frequency NMES modality could preferentially activate afferent pathways leading to a synaptic recruitment of motor units according to the size principle, which may reduce fatigability of evoked contractions (see Barss et al[47]) and result in a progressive increase in evoked force over time.[46] The latter phenomenon is often referred to as "extra" (or "central") force and has mainly been related to spinal mechanisms (eg, activation of persistent inward currents in spinal motoneurons).[46] Besides these effects on spinal circuitry, wide-pulse high-frequency NMES may modulate transcallosal communication[48] and lead to specific brain activation patterns as compared with conventional NMES.[49] Overall, both spinal and supraspinal structures might be targeted by the wide-pulse high-frequency NMES modality, even though its chronic effects on CNS pathways remain to be established.

Thus, NMES does not actually bypass the CNS, but results in a multitude of neurally mediated responses—at both spinal and supraspinal levels—that contribute substantially to force generation.

What are we overlooking? A methodological perspective

The main drawbacks of NMES for researchers, clinicians, and patients are as follows: (1) excessive discomfort; (2) limited muscle recruitment; (3) premature fatigue; and (4) problematic poor dosability (for review see Maffiuletti[6]). Researchers have long attempted to optimize stimulation parameters with the aim to downplay these limitations, but with partial success. In this section, we argue that too much emphasis was given to externally controllable stimulation parameters while the major determinant of NMES effectiveness is the intrinsically determined muscle tension generated by the current (ie, evoked force). We therefore contend that electrically evoked force control (and modulation) is the single most important requirement for the clinical success of NMES therapy.

Among various stimulation parameters, pulse characteristics such as shape, duration, frequency, and intensity as well as temporal distribution of the current (duty cycle) have long been manipulated to maximize evoked force, attenuate discomfort, and minimize fatigue.[27-35] However, the results were extremely inconsistent, probably owing to the large heterogeneity in protocols and populations. Similarly, the influence of electrode type,[50] size,[51,52] and location[52-54] on perceived discomfort and evoked force has been extensively investigated. However, given the large interindividual variability in motor point locations,[55] an individualized approach is advocated for optimal electrode positioning.[56]

Although NMES has certainly benefited from the above-cited studies aiming at optimizing stimulation parameters, its clinical use is still extremely diverse and a need for standardization was already asked 30 years ago.[57] Among the myriad of possibilities offered by the commercially available stimulators, the clinician should operate within evidence-based "ranges" (rather than fixed numbers) for the main pulse characteristics. As such, biphasic rectangular pulses of 100 to 400μs delivered with a stimulation frequency of 50 to 100Hz[58] at the highest tolerated current intensity[59] seem adequate to maximize quadriceps muscle tension. However, we support the idea that the effectiveness of NMES relies more on individual intrinsic neuromuscular properties (eg, superficial motor nerve branching), which determine the level of tension generated by a muscle, than on externally controllable factors (eg, current characteristics).[50] Accordingly, there is increasing evidence that the effectiveness of NMES is proportional to the evoked force[60-63]—usually expressed as a percentage of the maximum voluntary contraction (MVC) force and referred to as NMES training intensity—which has also been shown to be proportional to the amount of muscle mass activated by NMES.[64] For example, in the seminal study of Lai et al,[61] the quadriceps muscle was stimulated for 3 weeks at 2 NMES training intensities (25% and 50% of the MVC force) in 2 groups of able-bodied volunteers. NMES effectiveness, referred to as the treatment-induced gain in maximal strength, was linearly related to NMES training intensity (24% and 48% in respective groups). Therefore, NMES training intensity, not current intensity or any other stimulation parameter, should be considered as the main determinant of NMES effectiveness.

Interestingly, this "dose-response" relation between NMES treatment−induced strength gains and NMES training intensity has been confirmed in various clinical populations, such as after anterior cruciate ligament reconstruction[10] and total knee arthroplasty[65] as well as in patients with chronic obstructive pulmonary disease.[66] As an arbitrary rule, the so-called therapeutic window range (ie, the NMES training intensity required to achieve treatment goals) has been suggested to be between 25% and 50% of the MVC force for patients with orthopedic problems,[67] between 15% and 25% of the MVC force for patients with chronic obstructive pulmonary disease,[68] and probably even less for patients in the intensive care unit.[69,70] However, we acknowledge that expressing the NMES-evoked force as a fraction of the MVC force is not always rigorous (eg, for weak patients) or even possible (eg, for some critically ill patients), but clinically acceptable solutions exist: (1) using normative data for MVC stratified by condition, age, and sex; (2) delivering NMES at a percentage of the individual motor threshold or of the evoked peak twitch[71,72]; and/or (3) implementing subjective grading scales/criteria to ensure that an adequate level of tension is generated (see section on application perspective).[73,74]

Thus, it is strongly recommended to individually monitor NMES-evoked force during $\geq$1 sessions of a treatment and to express it as a function of the MVC force whenever possible, with the ultimate goal to attain the highest possible NMES training intensity. This will increase the likelihood of successful NMES treatment or, alternatively, allow the early identification of patients who are not likely to respond to NMES adequately (see next section).

What are we overlooking? An application perspective

The usual drive toward greater complexity with medical interventions needs to be tempered by the practical issues of clinical implementation. As such, the application of NMES therapy needs to be readily achievable in a real-world clinical setting, focusing on patients who are most likely to achieve benefits while respecting evidence-based practice. We believe that a more systematic approach to NMES therapy should necessarily encompass these 2 components for an optimal application in clinical populations: (1) identifying patients who are more likely to respond to the treatment (responders) on the basis of their individual level of tolerance to NMES and (2) identifying the patient-specific impairment and implementing the best treatment protocol for addressing the impairment (impairment-based NMES).

Responders to NMES and tolerance

Tolerance to NMES is extremely individual specific.[75] It is likely that a nonnegligible proportion (probably ∼10%) of people with chronic disease and able-bodied elderly adults do not tolerate NMES,[76,77] and consequently they do not respond well to NMES treatment. Differences in age, sex,[78] body composition,[79] body impedance,[75] and pain tolerance are known contributors to the ability to sustain high NMES training intensities in the general population. It is also likely that muscle fatigue occurring during and after a NMES session[80] is involved in low tolerance to NMES. We previously tried to expressly identify the physiological parameters of tolerance to NMES in patients with chronic obstructive pulmonary disease.[77] Patients were fully familiarized with NMES, and then completed 7 treatment sessions independently at home. When they returned to the laboratory for an additional treatment session, we looked at the individual propensity to increase current intensity on their own at home. High fitness level, high fat-free mass, low systemic inflammation (ie, low circulating levels of interleukin 6), and high tolerance to discomfort were predictors of sufficiently high tolerance to NMES to achieve training goals.[77] On the contrary, cardiorespiratory demand during a typical NMES session was low and unrelated to NMES tolerance.

Impairment-based NMES: How a treatment algorithm can help

We have recently proposed a 2-phased treatment algorithm to aid clinicians in applying and monitoring NMES therapy after knee surgery.[81] Briefly, the algorithm emphasizes the reeducation of the affected neural pathways to supplement impaired neural activation. This is achieved by delivering adequate training doses to the quadriceps muscle when activation deficits are most pronounced (eg, early after knee surgery). As such, NMES should be performed daily (or even multiple times per day, ie, high volume) until neural activation deficits have largely resolved (treatment phase 1). Patients should be encouraged to use high-intensity NMES, with stimulation amplitudes set at the highest tolerable level, because muscle force production increases linearly with current intensity.[82] Clinicians and patients should be aware that current intensity may need to be increased periodically to accommodate improved tolerance or factors such as adiposity or swelling, which can result in increased impedance and limited contractile force.

Ideally, the therapist should formally assess treatment response, tolerance, and patients' independence and comfort with operation of the NMES device within 1 to 2 weeks of initiation of NMES. A key factor in determining the appropriateness of therapy is assessing the response of the quadriceps muscle to NMES by verifying that a full, sustained, tetanic contraction is generated (no fasciculation observed on visual inspection) with visual or palpable evidence of superior patellar glide.[73] This step is essential to provide an indication of whether therapeutic doses are likely to be achieved (see section on methodological perspective). If these criteria are not met, the NMES program may not achieve therapeutic doses; thus, it should be better discontinued and alternative rehabilitation strategies (eg, biofeedback) should be considered.

Neural activation deficits should resolve with the use of NMES therapy. Therefore, patients should be periodically reevaluated to determine whether a high-volume, high-intensity approach is still warranted. The main risk of continued high-volume therapy is pronounced muscle fatigue, which may result in reduced muscle force (and a corresponding reduction in the training dose delivered to the muscle) as well as a small but present possibility of muscle damage. Once a patient has progressed through treatment phase 1, a low-volume, high-intensity approach is recommended, targeting muscle hypertrophy rather than neural activation deficits (treatment phase 2). Here, the goal is still to supply the muscle with high-intensity NMES therapy, but with longer rest intervals between consecutive sessions to allow adequate recovery (eg, once daily or alternate days).

The clinical implementation of such a treatment algorithm has the potential to improve the success of NMES therapy. We believe that a similar impairment-based approach should be encouraged for different patient populations in an attempt to reduce the heterogeneity in individual response to NMES therapy and, in turn, to better standardize and monitor the clinical application of NMES.

Conclusions

Contrary to other forms of electrotherapy such as transcutaneous electrical nerve stimulation, NMES is not universally used in clinical settings. This is probably due to the dissonance between the approach often followed by researchers and the practical needs of a clinician. As elegantly discussed by Watson,[83] the researchers' theoretical approach implies 3 different and consecutive phases: (1) delivering energy by means of a device; (2) changing ≥1 physiological events; and (3) expecting a therapeutic effect. In contrast, the practical needs of a clinician would best be achieved by reversing the researchers' approach: (1) identifying the patient's problem; (2) stimulating specific physiological processes (targeting the problem); and (3) selecting the best modality and dose depending on the problem. A multitude of NMES studies have been published in the past few years, but their clinical relevance/utility is quite limited because the researchers' approach was embraced. For example, a common approach in most of these studies was to modify 1 stimulation parameter while looking at selected physiological variables, such as evoked force, to infer on the potential effectiveness of a hypothetical NMES treatment.

In the present narrative review, we hoped to call into question this prevailing model of NMES use against the overlooked clinicians' approach. We therefore contend that the crucial steps for ensuring the clinical effectiveness of a NMES-based treatment are the following: (1) identifying the neuromuscular impairment with clinical assessment and (2) implementing algorithm-based NMES (see section on application perspective) while (3) properly dosing the treatment with tension-controlled NMES (see section on methodological perspective) and eventually amplifying the neural effects of NMES (see section on neurophysiological perspective).

Not only this approach will prove useful to the clinicians interested in the application of NMES therapy with their patients, but it will also help reduce the heterogeneity in response to NMES that is classically observed in research studies. For example, early identification of nonresponders through the evaluation of individual tolerance to the current is fundamental to the success of the treatment (NMES therapy may not work for every patient). Another source of heterogeneity is related to the infinite combination of NMES protocols,[7,16,17,19,21,22,24-26]—that is, stimulation parameters, current types (see Vaz et al[84]), settings, and devices—while actually it was suggested >25 years ago that NMES effectiveness depends more on individual intrinsic neuromuscular properties, such as superficial motor nerve branching, than on externally controllable factors, such as current characteristics.[50] Finally, we would like to reiterate that evoked force or NMES training intensity is the only valid indicator of NMES treatment dose; therefore, its control (and modulation) certainly represents the most important methodological requirement for the clinical success of NMES therapy.

In conclusion, on the basis of the general content of this article we propose a noncomprehensive list of practical recommendations for an optimal and more consistent application of NMES therapy to restore or preserve quadriceps muscle function in the clinical context.

1. Use pulse frequencies in the range of 50 to 75Hz, pulse durations in the range 100 to 400μs, and highest-tolerable intensities to maximize force production.
2. Constant-current stimulators that allow at least 100mA of intensity are often necessary, especially for overweight patients or in the presence of swelling.
3. Electrodes should be large and possibly adapted to the size of the thigh to minimize current density and maximize patient comfort and muscle recruitment.
4. Electrodes should be placed as far apart on the quadriceps muscle belly as possible, ideally also on motor points.
5. Outline electrode location with a marker to help patients with electrode placement, or use a NMES device with the wrap system and embedded electrodes.
6. Contracting quadriceps muscle while the stimulator is on may increase patient tolerance of higher intensities in some individuals.
7. When patients are in control of the NMES unit intensities themselves, they often develop more of a tolerance for stimulation.
8. Modifying electrode placement and knee/hip joint angles slightly from session to session may optimize the recruitment of various muscle parts.
9. Therapists need to measure (whenever possible) or at least see a visible muscle contraction for there to be any benefits.
10. Exclude patients not able to generate electrically evoked forces >15% of the MVC force within 1 to 2 weeks (nonresponders).

Keywords

Electric stimulation; Muscle strength; Quadriceps muscle; Rehabilitation

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